CASE DESCRIPTION

A male neonate was born to a 35-year-old mother at an outside hospital at 39 1/7 weeks gestation via emergency cesarean section due to decreased fetal movements. The infant had respiratory distress secondary to meconium aspiration and was noted to have a large, distended abdomen at birth. Subsequent ultrasound confirmed hepatosplenomegaly with no evidence of liver mass or ascites. By report, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were initially within the reference intervals, but the patient had a prolonged INR (international normalized ratio) and hypoalbuminemia, supporting liver dysfunction. The infant was transferred to our institution for specialized care owing to hepatosplenomegaly, hypoglycemia, and coagulopathy of unknown etiology. On admission, the infant was additionally noted to be mildly pancytopenic, with increased lactate and ammonia. Initially, infectious etiologies were of primary concern given the history of meconium aspiration and the history of hepatosplenomegaly, which may be a presenting feature in patients with congenital infection. However, an extensive infectious disease workup was negative and included screens for hepatitis A, B, and C, HIV, herpes simplex virus, cytomegalovirus, Epstein–Barr virus, parvovirus, enterovirus, toxoplasmosis, and blood, urine, and stool cultures.

Hemophagocytic lymphohistiocytosis (HLH), although rare, was also a diagnostic consideration, as it can present with hepatosplenomegaly, coagulopathy, and pancytopenia, which were seen in this patient. However, the patient’s pancytopenia resolved and the patient lacked additional features of HLH such as hypertriglyceridemia and hyperferritinemia.

Given the patient’s presentation of hepatosplenomegaly, hypoglycemia, and increased lactate and ammonia, an inborn error of metabolism was also part of the initial differential diagnosis. To screen broadly for metabolic disorders, plasma amino acids, urine organic acids, and plasma acylcarnitines were ordered stat while newborn screen results were pending. The clinical team was then called by the laboratory regarding the urine organic acid screen results and informed that although the overall urine organic acid profile was unremarkable, they noted a significant additional peak that identified as vanillylmandelic acid (VMA), and recommended quantification by a more specific method if clinically indicated. VMA and homovanillic acid (HVA) are catecholamine metabolites that are increased in patients with catecholamine-secreting tumors such as neuroblastoma, pheochromocytoma, and other tumors of neural crest origin. Given the lack of a mass on imaging studies of this patient, a malignant process was not high on the differential. Despite this, the team proceeded with the recommendation to specifically quantify HVA and VMA given the lack of a diagnosis in this patient at the time. Specific quantification demonstrated substantial increases in both urine VMA (430 mg/g creatinine, reference interval, 0 – 32.8 mg/g creatinine) and HVA (432.5 mg/g creatinine, reference interval, 0 – 17.6 mg/g creatinine).

CASE DISCUSSION

Neuroblastoma is a developmental tumor presenting in young children that originates from immature sympathetic ganglion cells, with the capacity to synthesize and secrete catecholamines (1). As the most common cancer in infants less than 1-year-old, about 700 new cases of neuroblastoma are reported each year in the US, with an average age of diagnosis around 1–2 years of age (www.cancer.org, 2015). Neuroblastoma, an extracranial cancer, can arise anywhere throughout the sympathetic nervous system, with the adrenal glands and abdomen/retroperitoneum being the most common primary sites of origin (2). In this patient with a distended abdomen, a primary tumor was never identified despite repeated im-

QUESTIONS TO CONSIDER

1. What is in the differential diagnosis for a newborn with hepatomegaly?
2. Taken together with the patient’s clinical presentation, what diagnosis do the HVA and VMA results suggest?
3. What additional tests or procedures are needed to establish the diagnosis in this patient?
aging studies—the only initial evidence hinting at the potential for neuroblastoma was the increase in catecholamine metabolites HVA and VMA in urine. Thus, neuroblastoma became part of the differential and a subsequent ultrasound-guided percutaneous liver biopsy was performed. Microscopic examination of the liver biopsy demonstrated metastatic neuroblastoma with approximately 75% of the liver parenchyma involved. It is estimated that only 1% of neuroblastoma cases have an unknown primary tumor site (3).

In neuroblastoma, neural crest cells forming the tumor mass express enzymes responsible for catecholamine (dopamine and norepinephrine) metabolism. Relevant catabolic products include HVA derived from dopamine and VMA derived from norepinephrine. Both HVA and VMA can be detected in urine in increased amounts in neuroblastoma patients. Although standard practice recommends measurement of these metabolites in 24-h urine collections, studies have demonstrated that measurement from single random urine samples provides equivalent results, and thus the challenges of obtaining 24-h collections from children can be avoided (4). As biomarkers for the diagnosis of neuroblastoma, HVA, and VMA together have a high diagnostic specificity, ranging from 96% to >99% (4). The diagnostic sensitivity of these markers is more variable (66%–100%), with lower sensitivities in patients with early stage disease and lower catecholamine-producing tumor burden leading to an increase in false negatives (4).

Although urine catecholamines are increased in >90% of neuroblastomas, diagnostic criteria ultimately require histopathologic confirmation of tumor (1). Specifically, international criteria for diagnosis of neuroblastoma require either: a) unequivocal histologic evidence from tumor tissue with or without immunohistology, electron microscopy, or increased catecholamines or metabolites; or b) unequivocal histologic evidence from bone marrow and increases in catecholamines or their metabolites (5). Following diagnosis, CT and/or MRI scans, bilateral bone marrow aspirates, and biopsies are recommended for assessment of the primary tumor and potential metastases. Additionally, because metaiodobenzylguanidine (MIBG) selectively concentrates in >90% of neuroblastomas, MIBG scintigraphy is also required for staging (6). Currently there are 2 published consensus staging systems for neuroblastoma patients: the more widely used INSS (International Neuroblastoma Staging System) provides postsurgical staging guidelines, whereas the INRG (International Neuroblastoma Risk Group) staging system classifies neuroblastoma patients before treatment or surgery (see Tables 1 and 2) (5, 7). Once disease stage is established, additional biological and clinical variables such as patient age, tumor histology and ploidy, and genetic abnormalities [most notably MYCN (v-my c avian myelocytomatosis viral oncogene neuroblastoma derived homolog) amplification] are used for further risk stratification (6).

The main clinical presentation in this patient on admission was hepatomegaly. Hepatomegaly has a broad

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with the primary tumor may be positive).</td>
</tr>
<tr>
<td>2A</td>
<td>Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically.</td>
</tr>
<tr>
<td>2B</td>
<td>Localized tumor with or without complete gross excision, with ipsilateral nonadherent lymph nodes positive for tumor microscopically. Enlarged contralateral lymph nodes must be negative microscopically.</td>
</tr>
<tr>
<td>3</td>
<td>Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.</td>
</tr>
<tr>
<td>4</td>
<td>Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S).</td>
</tr>
<tr>
<td>4S</td>
<td>Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow (limited to infants &lt;1 year of age).</td>
</tr>
</tbody>
</table>

* Adapted from Brodeur et al. (5).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>Localized tumor not involving vital structures as defined by the list of image-defined risk factors* and confined to one body compartment</td>
</tr>
<tr>
<td>L2</td>
<td>Locoregional tumor with presence of one or more image-defined risk factors*</td>
</tr>
<tr>
<td>M</td>
<td>Distant metastatic disease (except stage MS)</td>
</tr>
<tr>
<td>MS</td>
<td>Metastatic disease in children younger than 18 months with metastases confined to skin, liver, and/or bone marrow</td>
</tr>
</tbody>
</table>

* Adapted from Monclair et al. (7).

* Detailed list of image-defined risk factors can be found in Monclair et al. (7).
After undergoing treatment, the patient’s clinical phosphamide, and doxorubicin was started shortly thereafter chemotherapy with etoposide, carboplatin, cyclo-

apy could worsen the patient’s liver function, radiation neuroblastoma. Since there was concern that chemother-
sies) was deferred to allow for immediate treatment of the (MIBG scan, bilateral bone marrow aspirates, and biop-

Given the critical state of the patient, further staging 
renal dysfunction, hepatic failure, and coagulopathy. Ultimately, liver biopsy led to the diagnosis of an uncommon cause of hepatomegaly in a neonate—infiltration secondary to metastatic neuroblastoma. Clinical presentation in patients with neuroblastoma is highly variable but will generally fall into 1 of 3 clinical categories based on disease stage: localized tumors, metastatic disease, and 4S disease (6). Stage 4S typically has a favorable prognosis and is unique amongst metastatic tumors in that it will often spontaneously regress without therapy (6). However, infants <2 months old with stage 4S disease will often present with frank hepatomegaly secondary to rapidly progressive infiltration of the liver with neuroblas-
toma leading to respiratory compromise, renal dysfunction and coagulopathy (6, 9). Therefore, in this patient, although a primary tumor was never identified, it was felt the patient was best classified as stage 4S due to age, hepatomegaly secondary to metastatic neuroblastoma, and no evidence of metastases in other organs.

CASE FOLLOW-UP

In this diagnostically challenging patient, the presence of increased VMA was initially noted on a urine organic acid screen, and a subsequent specific quantitative measurement recommended by the laboratory for both VMA and HVA was essential for alerting clinicians to the possibility of neuroblastoma. Diagnosis of neuroblastoma was ultimately confirmed due to the subsequent liver biopsy demonstrating extensive involvement by metastatic neuroblastoma with favorable histology and nonamplification of MYCN, and the patient was categorized as stage 4S as described previously. At the time of diagnosis, the patient was unstable and critically ill, intu-

bated and sedated secondary to respiratory failure, with renal dysfunction, hepatic failure, and coagulopathy. Given the critical state of the patient, further staging (MIBG scan, bilateral bone marrow aspirates, and biop-
sies) was deferred to allow for immediate treatment of the neuroblastoma. Since there was concern that chemother-

apy could worsen the patient’s liver function, radiation therapy was initiated first to reduce disease burden and then chemotherapy with etoposide, carboplatin, cyclo-

phosphamide, and doxorubicin was started shortly there-
after. While undergoing treatment, the patient’s clinical course was complicated by acute kidney injury requiring hemodialysis, tumor lysis syndrome, worsening coagu-
olphathy, bone marrow suppression secondary to chemo-
therapy, ascites, and urinary tract infection over the sub-
sequent 3 months. Despite the difficult clinical course, measurements of urinary HVA and VMA decreased to 10.5 mg/g creatinine (reference: 0–32.8 mg/g creatinine) and 39.8 mg/g creatinine (reference: 0–17.6 mg/g creati-
nine), respectively, indicating a good response to radiation and chemotherapy. A second liver biopsy 3 months after diagnosis confirmed treatment efficacy, with the volume of neuroblastic cells reduced to only 2%–5% of the liver parenchyma. Additionally, a staging bone marrow biopsy demonstrated no evidence of neuroblastoma, and a MIBG scan showed no evidence of neuroblastoma outside the liver. At 5 months of age, the patient was stable enough for transfer to another care facility closer to home.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or
Commentary

Irene De Biase1,2*

Sometimes, when we hear hoof beats, we should think about zebras. This report describes an unusual clinical presentation for neuroblastoma, a fairly common childhood malignancy. Neonatal neuroblastomas (detected within the first month of life) are rare, accounting for <5% of all cases. A primary tumor is not found in fewer than 1% of neuroblastoma patients. This patient presented within the first hour of life with respiratory distress and distended abdomen due to severe hepatomegaly. Because imaging studies failed to identify a primary lesion, malignancy was low on the differential. An increase in VMA excretion was detected by routine urine organic acid analysis, performed to exclude a metabolic cause of hepatomegaly, and triggered specific follow-up. Quantification of HVA and VMA and a liver biopsy confirmed metastatic neuroblastoma, classified as stage 4S.

This case illustrates the importance of including rare clinical presentations, not just rare conditions, in the differential diagnosis. Neuroblastoma should not be excluded despite negative imaging studies. Moreover, in my opinion, serendipity plays a bigger role in patients’ care that we would like. HVA and VMA are sensitive and specific biomarkers for this condition and are routinely measured when neuroblastoma is suspected. These compounds can also be detected by urine organic acid analysis, as demonstrated by this report. However, the substantial increase observed in HVA with the specific test was not detected by urine organic acid analysis, and isolated increases in HVA or VMA can be overlooked, if there is no clinical suspicion. Good communication between the laboratory and the clinical team facilitates the diagnostic process. In infants with metastatic neuroblastoma in stage 4S, disease burden complicates the otherwise benign progression. Prompt therapeutic intervention is lifesaving in these cases and, indeed, it was critical for this patient’s good outcome.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.

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